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Moclobemide: Therapeutic Use and Clinical Studies

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ABSTRACT

Moclobemide is a reversible inhibitor of monoamine-oxidase-A (RIMA) and has been extensively evaluated in the treatment of a wide spectrum of depressive disorders and less extensively studied in anxiety disorders. Nearly all meta-analyses and most comparative studies indicated that in the acute management of depression this drug is more efficacious than placebo and as efficacious as tricyclic (or some heterocyclic) antidepressants or selective serotonin reuptake inhibitors (SSRIs). There is a growing evidence that moclobemide is not inferior to other antidepressants in the treatment of subtypes of depression, such as dysthymia, endogenous (unipolar and bipolar), reactive, atypical, agitated, and retarded depression as with other antidepressants limited evidence suggests that moclobemide has consistent long-term efficacy. However, more controlled studies addressing this issue are needed. For patients with bipolar depression the risk of developing mania seems to be not higher with moclobemide than with other antidepressants. The effective therapeutic dose range for moclobemide in most acute phase trials was 300 to 600 mg, divided in 2 to 3 doses. While one controlled trial and one long-term open-label study found moclobemide to be efficacious in social phobia, three controlled trials subsequently revealed either no effect or less robust effects with the tendency of higher doses (600 – 900 mg/d) to be more efficacious. Two comparative trials demonstrated moclobemide to be as efficacious as fluoxetine or clomipramine in patients suffering from panic disorder. Placebo-controlled trials in this indication are, however, still lacking.

A relationship between the plasma concentration of moclobemide and its therapeutic efficacy is not apparent but a positive correlation with adverse events has been found. Dizziness, nausea and insomnia occurred more frequently on moclobemide than on placebo. Due to negligible anticholinergic and antihistaminic actions, moclobemide has been better tolerated than tri- or heterocyclic antidepressants. Gastrointestinal side effects and, espe-

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cially, sexual dysfunction were much less frequent with moclobemide than with SSRIs. Unlike irreversible MAO-inhibitors, moclobemide has a negligible propensity to induce hypertensive crisis after ingestion of tyramine-rich food ("cheese-reaction"). Therefore, dietary restrictions are not as strict. However, with moclobemide doses above 900 mg/d the risk of interaction with ingested tyramine might become clinically relevant. After multiple dosing the oral bioavailability of moclobemide reaches almost 100%. At therapeutic doses, moclobemide lacks significant negative effects on psychomotor performance, cognitive function or cardiovascular system. Due to the relative freedom from these side effects, moclobemide is particularly attractive in the treatment of elderly patients.

Moclobemide is a substrate of CYP2C19. Although it acts as an inhibitor of CYP1A2, CYP2C19, and CYP2D6, relatively few clinically important drug interactions involving moclobemide have been reported. It is relatively safe even in overdose. The drug has a short plasma elimination half-life that allows switching to an alternative agent within 24 h. Since it is well tolerated, therapeutic doses can often be reached rapidly upon onset of treatment. Steady-state plasma levels are reached approximately at one week following dose adjustment. Patients with renal dysfunction require no dose reduction in contrast to patients with severe hepatic impairment.

Cases of refractory depression might improve with a combination of moclobemide with other antidepressants, such as clomipramine or a SSRI. Since this combination has rarely been associated with a potentially lethal serotonin syndrome, it requires lower entry doses, a slower dose titration and a more careful monitoring of patients. Combination therapy with moclobemide and other serotonergic agents, or opioids, should be undertaken with caution, although no serious adverse events have been published with therapeutic doses of moclobemide to date. On the basis of animal data the combined use of moclobemide with pethidine or dextropropoxyphene should be avoided. There is no evidence that moclobemide would increase body weight or produce seizures. Some preclinical data suggest that moclobemide may have anticonvulsant property.

INTRODUCTION

A preceding review (33) dealt with moclobemide's history, pharmacodynamic, and pharmacokinetic properties. This review article is primarily concerned with the therapeutic use, tolerability and safety of moclobemide. Based upon results of clinical studies, an appraisal of its place in the management of depression and anxiety disorders is attempted. This article extends and updates previously published comprehensive surveys on moclobemide (83, 85).

THERAPEUTIC USE

Depression

The efficacy and tolerability of moclobemide in depressive disorders have been investigated in controlled clinical trials on over 20,000 patients. After open pilot studies, a series of double-blind comparative studies were conducted to compare moclobemide with placebo and other antidepressants (216). Most studies employed a preliminary single-blind pla-

cebo phase lasting at least one week. Usually the duration of the prospective studies, described in more detail below, was 4 to 6 weeks and the dose of moclobemide ranged from 200 to 600 mg/d, administered after meals. Inclusion criteria were a major depressive episode according to DSM-III, DSM-III-R, DSM-IV, or ICD 9 together with a minimum score on one of the depression rating scales, i.e., the Hamilton depression rating scale (HAM-D) (104) or the Montgomery-Asberg depression rating scale (MADRS) (165). All studies employed at least one depression scale, usually HAM-D, together with a scale estimating the general efficacy, usually CGI (Clinical Global Impression of efficacy) (101). Main efficacy criteria were derived from these scales and from the number of premature discontinuations. A reduction of HAM-D ≥ 50% was usually required for an improvement of depressive symptoms and to separate responders from non-responders. The tolerability was assessed on the basis of frequency and severity of adverse clinical events (ACE) occurring during the studies, the number of premature terminations due to ACE and often on the basis of CGI of tolerability (101).

To achieve sufficiently high sample sizes most studies were performed as multi-center trials. From the statistical perspective, a well-designed dose-finding study with a placebo, an active control group and with three different doses of the test drug would require 5×100 to 5×200 patients (193). The large sample size is the likely reason why dose-finding studies are seldom conducted. The high cost of dose-range finding studies is, however, not a valid reason for not conducting them. The failure to conduct dose-range studies may lead to inappropriate treatment for a large numbers of patients. Only small dose-finding studies have been performed with moclobemide (42,119); their results suggested that in the treatment of depression 300 mg dose of moclobemide may be more beneficial than 150 mg. However, the differences between the treatment groups did not reach statistical significance (193). Most large double-blind trials with moclobemide were anticipatory and used doses of 300 to 600 mg/d of the drug. One large psychiatric practice study involving 712 outpatients suffering from major depression revealed an improvement with moclobemide (450 mg/d) in 65% of patients after 8 weeks of treatment (235).

COMPARISON WITH PLACEBO

Twelve randomized, double-blind studies compared moclobemide with placebo (14,34, 35,41,136,169,182,209,217,240,245,249). Nine of these studies, including the three largest studies (14,245,249), showed superior efficacy of moclobemide over placebo. The studies of Larsen et al. (136), Silverstone et al. (209), and Nair et al. (169) found that moclobemide was not superior to placebo.

In the study of Larsen et al. (136), moclobemide was compared with clomipramine and placebo in patients with major depressive episodes. Patients suffering from a non-endogenous type of depression according to the Newcastle-II criteria were excluded. Sixty depressed patients were allocated to either moclobemide, 300 mg, clomipramine, 150 mg, or placebo for a period of 6 weeks. Symptoms of depression improved in all groups and there was no significant difference between the treatments. Similarly, a multicenter study conducted by the UK Moclobemide Study Group involving 166 patients with major depressive episodes (DSM-III-R) revealed no significant differences between moclobemide (300 to 450 mg), imipramine (75 to 150 mg), or placebo (Table 1) (209).

TABLE 1. Randomized double-blind comparative trials with moclobemide and tricyclics or heterocyclics in adult patients with major depression — larger studies

Study	Sample size for moclobemide (*N*)	Dosage (mg)	HAM-D (mean ± S.D.)	Response rate (% of patients) M	T	P	Overall efficacy[a]	Overall tolerability[b]
Imipramine (33.3–200 mg)								
Baumhackl et al. 1989	181	300–600	25 ± 6[d]	58[c]	58[c]	–	M = T	M > T
Versiani et al. 1989	158	300–600	26 ± 5[d]	63[c]	68[c]	29[c]	M = T > P	P > M > T
Rimón et al. 1993	55	75–525	≥17[d]	71[c]	64[c]	–	M = T	M > T
Silverstone et al. 1994	72	450	25 ± 5	53[e]	50[e]	51[e]	M = T = P	M = P > T
Clomipramine (25–200 mg)								
Lecrubier and Guelfi 1990	64	300–600	at 25	63[e]	65[e]	–	M = T	M > T
Larsen et al. 1991	59	300	≥15	46[h]	72[h]	–	M < T	M > T
Guelfi et al. 1992	62	300–600	28 ± 4	66[g]	72[g]	–	M = T	M > T
DUAG 1993	57	400	at 24	19[f]	33[f]	–	M < T	M > T
Lecrubier et al. 1995	57	400–600	24 ± 4	63[a]	65[a]	–	M = T	M > T
Kragh-Sorensen et al. 1995	48	400	≥16	52[f]	37[f]	–	M = T	M > T
	23		11–15	48[f]	33[f]			
Jouvent et al. 1998	65	450	33 ± 5[i]	77[g]	61[g]	–	M = T	M > T
Amitriptyline (50–150 mg)								
Bakish et al. 1992	57	200–600	23	56[c]	60[c]	36[c]	M = T > P	M = P > T
Doxepin (100 mg)								
Philipp et al. 1993	169	240–580	≥18	52[c]	44[c]	–	M = T	M > T
Lingjaerde et al. 1995	30	400–600	at 13[i]	60[g]	78[g]	–	M = T	M > T
Nortriptyline (50–100 mg)								
Nair et al. 1995[k]	32	400	≥18	37[g]	46[g]	40[g]	M = P < T	M = P > T
Dothiepin (75–150 mg)								
Beaumont et al. 1993	170	450	>18	57[c]	70[c]	–	M < T	M > T
Maprotiline (75–100 mg)								
Steinmeyer et al. 1993	58	300–600	≥17	71[c]	78[c]	–	M = H	M > H
Gachoud et al. 1994	66	300–400	≥17	66[g]	59[g]	–	M = H	M > H

[a] Overall efficacy as derived from statistically significant differences between the groups with respect to primary efficacy criteria[b,e–h].

[b] Overall tolerability as derived from rates of adverse clinical effects and dropout rates.

[c] Reduction of HAM-D score ≥50% = responder; after 4–6 weeks of treatment.

[d] HAM-D, 21 items.

[e] HAMD-score reduced by ≥50 to <10, after 6 weeks.

[f] HAM-D score reduced to <7, after 6 weeks.

[g] Percentage of patients showing "good" or "very good" improvement in CGI, after 4–6 weeks.

[h] HAMD-score reduced to <9, after 6 weeks.

[i] Montgomery-Asberg depression rating scale.

[k] Studies in elderly.

Abbreviations: M, moclobemide; T, tricyclic antidepressants; H, heterocyclic antidepressant; P, placebo; HAM-D, Hamilton depression rating scale; CGI, Clinical Global Impression (of efficacy); DUAG, Danish University Antidepressiva Study Group.

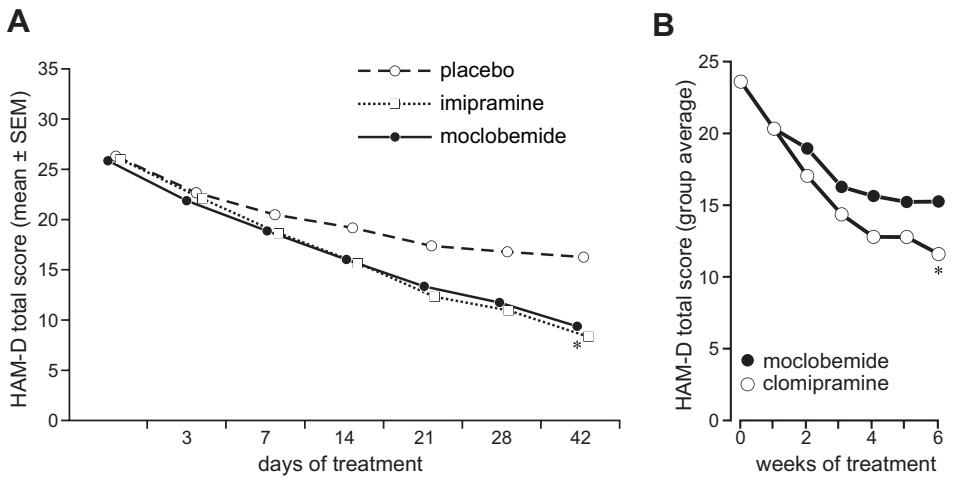

Fig. 1. Evolution of total HAM-D scores in two randomized, double blind trials comparing the efficacy of moclobemide and tricyclics in a major depressive episode. A: Reductions in HAM-D score emerged significantly greater in either moclobemide or imipramine group as compared to placebo group. No significant differences were found between the moclobemide and imipramine group. B: Reductions in HAM-D scores emerged significantly greater in the clomipramine than in the moclobemide group. * $P < 0.05$. A: Adapted from ref. 245, B: Adapted from ref. 51.

Seven small 4-week studies involving up to 60 patients with major depression revealed a significantly greater improvement of HAM-D ratings in the moclobemide treated groups than in the placebo groups (34,35,41,169,240,182,217). Dropout rates were reported to be significantly higher in the placebo groups. The largest placebo-controlled study was that of Versiani et al. (245). This three-way trial compared moclobemide, imipramine and placebo in a total of 490 patients with a major depressive episode (DSM-III). Approximately 50% of the patients in each group were diagnosed as suffering from endogenous depression according to the ICD-9 criteria. The duration of the trial was 6 weeks, the mean daily dose moclobemide was 475 mg, and of imipramine 147 mg. The study demonstrated a superiority of moclobemide and imipramine over placebo with no significant differences between the two active drugs (Table 1, Fig. 1A). Moclobemide and imipramine were equally effective in treating subtypes of depression (i.e., endogenous, neurotic, reactive).

Similar results were obtained in another three-way study by Bakish et al. (14) comparing moclobemide with amitriptyline and placebo in 173 patients with major depressive episodes (DSM-III-R) over a 6 week period. Mean doses of 492 mg moclobemide and 112 mg amitriptyline were used. Both, amitriptyline and moclobemide were significantly superior to placebo (Table 1) (14). In a more recent study, Versiani et al (249) found moclobemide significantly superior to placebo in the treatment of dysthymia.

In summary, in nine out of twelve studies moclobemide, at daily doses between 300 and 600 mg, was superior to placebo in the treatment of the major depressive episodes. Two studies failed to show either moclobemide (300 to 450 mg) or clomipramine/imipramine (75 to 150 mg) to be more effective than placebo (136, 209). One of the latter studies investigated only patients with non-endogenous depression (136). This subgroup responded to moclobemide (300 to 600 mg) or imipramine (100 to 200 mg) in the large study by Versiani et al. (245). All currently available meta-analyses revealed moclobe-

mide to be clearly superior to placebo, irrespective of the outcome measures applied (9,58,153).

COMPARISON WITH ANTIDEPRESSANTS

Tricyclic and Heterocyclic Antidepressants

Imipramine

In addition to the above mentioned studies of Versiani et al. (245) (Fig. 1A) and Silverstone et al. (209), moclobemide (300 to 600 mg) and imipramine (100 to 200 mg) were compared in a larger multicenter trial by Baumhackl et al. (22). Both drugs were judged effective according to the total HAM-D and CGI. The mean final improvement on the HAM-D was 52% in both groups (Table 1). Subgroup analyses found no difference in efficacy between moclobemide and imipramine in patients with endogenous depression (ICD-9). Furthermore, three smaller studies revealed no difference in the antidepressant activity of the two drugs (41,127,199).

Clomipramine

In addition to the three-arm study of Larsen (136), seven larger (Table 1) and five smaller trials compared the efficacy of moclobemide and clomipramine in depressed patients.

Guelfi et al. (98) investigated 129 patients with endogenous depression (ICD-9, Newcastle criteria) in a 6-week trial (300 to 600 mg moclobemide vs. 100 to 200 mg clomipramine). There were no significant difference between the treatment groups according to the total scores of the Montgomery-Asberg depression rating scale and CGI (Table 1). A complementary trial by Lecrubier and Guelfi (142) in 191 outpatients with non-endogenous depression treated with either of the two drugs for at least 6 weeks, found also no significant differences between the treatment groups according to the primary efficacy criteria (HAM-D, CGI). The onset of antidepressant activity was shorter with moclobemide (10.6 days) than with clomipramine (13.2 days). The mean drug doses were 478 mg/d moclobemide and 118 mg/d clomipramine (142). The results were confirmed in two more recent studies: one with nonmelancholic, nonpsychotic outpatients with a DSM-III major depressive episodes treated for 6 weeks to 3 months (143), and another with patients with a major depressive episode with focus on psychomotor retardation treated for over 4 weeks (117). In addition, Kragh-Sorensen et al. (131) found no difference in the antidepressant activity of the two drugs at the end of a 6-week-study.

In two trials, moclobemide's antidepressant activity has been reported to be inferior to that of clomipramine. Larsen et al. (137) treated 187 outpatients with either 300 mg moclobemide, 150 mg clomipramine or 30 mg isocarboxazide for 6 weeks. Moclobemide was found to be less effective than clomipramine (Table 1) and there was no evidence that it was specifically effective in a subgroup of patients with dysphoric depression. A similar outcome was reported in a multicenter study by the Danish University Antidepressant Group (51) in which moclobemide (2×200 mg/d) was compared with clomipramine (at doses up to 2×75 mg). In this trial 115 inpatients suffering from major depression were randomized to the two study groups. After 1 week of baseline placebo treatment (single

blind) the patients were treated with moclobemide for 6 weeks. Towards the end of the study a significant difference in favor of clomipramine was apparent in HAM-D (Fig. 1B, Table 1), especially in the depression/guilt and the sleep disturbance clusters (51). The investigators reported, a higher incidence of suicide in the patients treated with moclobemide. No significant differences between moclobemide and clomipramine were detected in the remaining five smaller trials (46,63,86,124,135).

Considering all comparative studies of moclobemide and clomipramine, Priest and Schmid-Burgk (193) suggested that both drugs are equally effective when clomipramine is used at 100 to 200 mg and moclobemide at 300 to 600 mg. Two larger studies found clomipramine to be superior to moclobemide (51,137) and the Danish University Antidepressant group reported a higher incidence of suicide in the moclobemide-group (51). However, these two studies are limited due to their fixed dose-schedules in the moclobemide groups.

Amitriptyline

Five studies comparing moclobemide with amitriptyline have been published. The largest was the three-arm study of Bakish et al. (14) which enrolled 173 patients. According to the CGI a "very good" or "good" response was found in 57% of the moclobemide- (200 to 600 mg), in 60% of the amityptyline- (50 to 150 mg) and in 35% of the placebo-treated patients. This finding was based on the number of patients in each group who achieved a ≥50% reduction in their total HAM-D score. There was no significant difference in the efficacy of the two active drugs, which were both significantly superior to the placebo (Table 1). Additional smaller comparative trials found also no significant differences in the antidepressant efficacy of the two drugs (78,173,175,180).

Other tri- and heterocyclics

Small studies comparing moclobemide with desipramine (87,220) or maprotiline (38, 88,139,224,243) did not show any difference in antidepressant efficacy of these drugs. Again, in a large study by Phillip et al. (189), no significant differences were detected between the antidepressant efficacy of doxepin (100 mg) and that of moclobemide (240 to 580 mg) (Table 1), although the onset of antidepressant action of moclobemide was shorter than that of doxepin (189). A smaller 6 week-trial confirmed the therapeutic equality of doxepin and moclobemide (147). In a large multi-center study involving patients in general practice dothiepin was reported to have a small, but significant advantage over moclobemide in the treatment of depression (24).

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs have been shown to be as effective, but better tolerated, than tricyclics in the treatment of major depression. Thirteen well-controlled trials comparing moclobemide with SSRIs have been published (19,31,36,72,73,91,91,134,150,151,184,198,257): nine of these trials involved comparison with fluoxetine, three with fluvoxamine and one with sertraline. Moclobemide was found to have similar efficacy in major depression as either of these SSRIs (Table 2).

Three studies reported that the onset of the antidepressant action of moclobemide was shorter than that of SSRIs. After 7 to 10 days of treatment the HAM-D scores or the CGI were significantly more improved in patients on moclobemide than on fluoxetine (31,91,

94). However, a recent meta-analysis of the data of 440 fluoxetine-treated and 437 moclobemide-treated patients provided by Hoffmann-La Roche revealed no significant difference in the time course of recovery between the two groups (219). The onset of improvement in the majority of cases occurred within the first two weeks of treatment (219). If the patients did not respond to the initial 150 mg dose of moclobemide, an increase in the dose to 300 mg resulted in a statistically significant improvement of CGI after 3 weeks of therapy (198).

With respect to subtypes, one study described moclobemide to be slightly superior to fluoxetine in the treatment of double depression (73). In this study HAM-D-response was significantly better in the moclobemide group, while CGI similarly improved in both treatment groups (73). Subgroup analysis in the large study of Lonnqvist et al. (150) revealed moclobemide to be as effective as fluoxetine in patients suffering from dysthymia. Patients with atypical depression had a significantly lower MADRS score on moclobemide than on fluoxetine at the end of the study, although the HAM-D scores were not sig-

TABLE 2. Randomized double-blind comparative trials with moclobemide and selective serotonin reuptake inhibitors (SSRIs) in adult patients with depression

Comparator drug Study	Sample size for moclobemide (*N*)	Diagnosis	Dosage (mg)	Response rate in %[a] M	S	Overall efficacy[b]	Overall tolerability[c]
Fluoxetine (20–40 mg)							
Williams et al. 1993	61	Major depression	300–600	72	59	M = S	M = S
Geerts et al. 1994	15	Major depression	300–600	67	77	M = S	M = S
Lonnqvist et al. 1994	102	Major depression	300–450	67	57	M = S	M = S
Lonnqvist et al. 1994	24	Atypical depression	300–450	67	55	M = S	M = S
Gattaz et al. 1995	27	Major depression	300–600	59	58	M = S	M = S
Reynaert et al. 1995	38	Major depression	300–600	47	48	M = S	M = S
Duarte et al. 1996	21	Double depression	300	71	38	M > S	M = S
Partonen et al. 1996	11	SAD	300–450	73	61	M = S	–
	63	Non-SAD		68	51		
Lapierre et al. 1997	61	Major depression	300–600	54	55	M = S	M > S
Fluvoxamine (100–200 mg)							
Barrelet et al. 1991	28	Major depression	300–450	59	57	M = S	M > S
Bougerol et al. 1992	65	Major depression	300–450	48	48	M = S	M = S
Bocksberger et al. 1993	19	Major depression (in elderly)	300–400	84	55	M > S	M = S
Sertraline (50–200 mg)							
Dönbak et al. 1995	15	Major/minor depression	300–600	76[d]	78[d]	M = S	M = S

[a] Reduction of HAM-D score ≥50% = responder, after 4–6 weeks of treatment.
[b] Overall efficacy as derived from statistically significant differences between the groups with respect to primary efficacy criteria ≥50% HAM-D reduction and/or improvement of CGI.
[c] Overall tolerability as derived from rates of adverse clinical effects and drop-out rates.
[d] response-rates after 13 weeks of treatment.
Abbreviations: S, SSRIs; M, moclobemide; SAD, seasonal affective disorder.

nificantly different in the two treatment groups (151). In seasonal affective disorder, moclobemide was as effective as fluoxetine (184).

Other Antidepressants Including MAO-Inhibitors

In a brief report of a comparative study with amineptine and moclobemide in endogenously depressed patients, both drugs showed clinical equivalence in terms of changes in total HAM-D and CGI. However, patients' self-rating scales of treatment benefit favored moclobemide, suggesting a greater incidence of anxiety associated with amineptine (154).

A larger trial including 268 patients compared moclobemide with toloxatone. Similar antidepressant efficacy was reported for the two RIMAs. It was noted, however, that improvement of depressive retardation was significantly better with moclobemide and that the onset of moclobemide action was faster (144).

Another trial compared moclobemide (300 to 600 mg) and pirlindole (150 to 300 mg) in 6-weeks-long trial. From a total of 116 patients, 111 were evaluable for efficacy. Either of the two drugs produced highly significant improvements in HAM-D, the Hamilton Anxiety Rating Scale and the MADRS from day 7 to day 42. After 42 days of treatment, an improvement of ≥50% in the HAM-D score was noted in 67 and 80% of patients in the moclobemide and pirlindole group, respectively (230).

Two larger trials comparing moclobemide with traditional MAO-inhibitors (trancylpromine and isocarboxazid) are available (107,137). These studies used relatively low doses of the drugs. Heinze et al. (107) reported that in 160 patients with unipolar or bipolar endogenous depression the antidepressant efficacy of moclobemide (150 to 300 mg/d) resembled that of tranylcypromine (15 to 30 mg/d). After 4 weeks, HAM-D total scores were reduced to 63 and 58% with moclobemide and tranylcypromine, respectively. Premature discontinuation of treatment was significantly more frequent in the tranylcypromine (15.4%) than in the moclobemide group (4.9%) (107). Larsen et al. (137) reported that after 6 weeks of treatment 300 mg moclobemide produced a significantly smaller reduction in mean HAM-D than 30 mg isocarboxazid.

META-ANALYSES AND ANALYSES IN DIFFERENT SUBTYPES OF DEPRESSION

A recent meta-analysis included 3318 patients in 47 studies comparing moclobemide with either another antidepressant or placebo (153). As usual, the response was defined as the percentage of patients achieving either a 50% reduction in HAM-D (104) or a final Clinical Global Impression (CGI, 101) score of 1 or 2 ("markedly improved" or "very much improved"). In the modified "intent to treat" samples (ITT) moclobemide was found to be significantly more effective than placebo and as effective as tricyclic antidepressants or SSRIs in the acute management of major depression (most studies lasted 4 to 6 weeks). These findings were valid when only study completers (AT) were analyzed. The response rate to moclobemide in all studies was 58 ± 2.3% (ITT) and 67 ± 2.3% (AT) with no significant difference between moclobemide and the active comparators. This finding was valid for both, inpatients and outpatients (153). It has been reported that at higher doses moclobemide might have better efficacy in more severe depression. Furthermore, it was

suggested that moclobemide may be somewhat less effective, but better tolerated, than classical MAO-inhibitors, such as phenelzine and tranylcypromine (153).

Classical MAO-inhibitors are considered not very effective in endogenous depression, but recommended for the treatment of atypical depression (194) and neurotic/reactive depression (185). Therefore, some earlier meta-analyses investigated the effects of moclobemide in various subtypes of depression (9–12,58). In these meta-analyses, the efficacy of moclobemide was similar to that of tricyclics in unipolar and bipolar disorders, dysthymia, as well as in atypical and double depression. In meta-analysis involving 2371 depressed patients from 38 well controlled studies the response rates to moclobemide were as follows: 66% in unipolar endogenous depression, 57% in bipolar depression, 47 to 66% in patients with dysthymia and 43% in reactive depression (10,11) (Table 3). It was suggested that severe depressives with psychotic features should be treated with higher moclobemide doses, ≥450 mg/d (12,153).

In another meta-analysis that included 2416 depressed patients from 40 studies, moclobemide was described to be equal in efficacy to imipramine or sedative antidepressants (amitriptyline, mianserin, maprotiline) in the treatment of agitated-anxious depressed patients (58). All antidepressants were clearly superior to placebo, irrespective of the outcome measures applied. Co-medication with benzodiazepines did not influence the overall efficacy of either moclobemide or other antidepressants in this patient population (58).

*TABLE 3. Efficacy of moclobemide in different diagnostic and syndromal subtypes of depression**

Diagnostic subgroup of depression	Number of patients (*N*)	Response rate[a] (%)	Global assessment of efficacy[b] (%)			
			0	+	++	+++
Unipolar	573	66	18	16	33	34
Bipolar	104	57	22	17	34	27
Neurotic	218	52	22	19	27	31
Reactive	68	43	29	12	29	28
Dysthymia						
4 weeks	70	47	9	17	53	21
8 weeks	70	66	20	14	16	50
Double depression						
4 weeks	38	66	6	13	53	26
8 weeks	38	76	10	5	24	61
Agitated depression	101	58	15	10	43	32
Retarded depression	588	56	23	15	28	34
Psychotic depression	316	58	25	15	28	32
Non-psychotic depression	899	58	18	17	35	30
Atypical depression	21	62	10	10	47	33
Patient group						
Inpatient	535	57	21	19	33	28
Outpatient	678	60	19	15	34	33

[a] Reduction of the HAM-D score ≥50% responder.
[b] Four-point efficacy scale, from 0 (no efficacy) to +++ (high degree of efficacy) (10).
* Adapted from ref. 11.

Several studies revealed an earlier onset of antidepressant response with moclobemide (during the first 2 weeks of treatment) if compared with tri- and heterocyclic antidepressants (142,143,189,243). This was interpreted to result primarily from the non-sedative action of moclobemide. However, a similar more rapid onset of action of moclobemide has been reported also in comparative study with fluoxetine (31,91,94). The question arises, therefore, whether the more rapid onset of action could result from an earlier effect on negative symptom dimensions of major depression, such as anhedonia, blunted affect and retardation. A study addressing this question revealed that moclobemide (450 mg, $n = 65$), unlike clomipramine (150 mg, $n = 59$) significantly improved these negative symptoms at days 7 and 10 of treatment (117). The overall efficacy at the end of the 4-week trial period was similar in both groups (117). However, a greater attrition rate due to a lack of efficacy was found with moclobemide (10 vs. 3) in this trial (117). Meta-analyses could not confirm an earlier antidepressant response on moclobemide (153,219).

A short review about moclobemide in dysthymia (188) listed 3 small, controlled studies on depressive patients fulfilling the DSM-III-R dysthymia criteria. These studies suggested moclobemide to be effective in dysthymia and double depression (35,73,248). This finding was confirmed in a larger subsequent trial enrolling 315 outpatients. After 8 weeks of treatment the percentage of patients who no longer fulfilled the DSM-III-R criteria was significantly higher on moclobemide (60%, 674 ± 117mg/d) or imipramine (49%, 219 ± 45 mg/d) than in the placebo group (22%) (Table 4) (249). A significant superiority of moclobemide or imipramine over placebo was also found in double depression, as well as in early and late onset varieties (249). Another small trial in patients with dysthymia showed that moclobemide in combination with interpersonal psychotherapy was not significantly superior to moclobemide in combination with routine clinical management (61).

Patients with reversed antidepressive symptoms, characteristic of atypical depression, were found to benefit from moclobemide in a small 4-weeks long trial (215).

A recent controlled 8-week study on 156 patients suffering from bipolar depression moclobemide (450 to 750 mg/d) was as effective as imipramine (150 to 250 mg/d)

TABLE 4. Controlled 8-week trials comparing moclobemide with imipramine in patients suffering from dysthymia or bipolar depression

	Sample size (*N*)			Dosage		Response rates (%)[a]			Overall	Overall
Study	M	I	P	(mg/d)	Diagnosis	M	I	P	efficacy[b]	tolerability[c]
Versiani et al. 1997	108	103	104	674 ± 117	Dysthymia	71	69[d]	30	M = I > P	M = P > I
Silverstone et al. 2001	81	75	–	450 – 750	Bipolar depression	46	53[e]	–	M = I	M > I

[a] Reduction of the HAM-D score ≥50% = responder.
[b] overall efficacy as derived from statistically significant differences between the groups with respect to primary efficacy criteria: ≥50% HAM-D reduction and/or improvement of CGI.
[c] Overall tolerability as derived from rates of adverse effects and drop-out rates.
[d] Imipramine 219 ± 45 mg/d.
[e] Imipramine 150–250 mg/d.
Abbreviations: M, moclobemide; I, imipramine; P, placebo.

(Table 4) (210). Two patients on moclobemide (3.7%) and six patients on imipramine (11%) were withdrawn because of the development of manic symptoms (210). Other observations suggested that the risk of development of mania in patients with bipolar depression is not higher with moclobemide than with other antidepressants (12,109,235).

LONG-TERM TREATMENT

Long-term treatment of depression can be subdivided into periods of continuation and maintenance (133,165,232,260). Continuation treatment should prevent the relapse of a currently treated depressive episode and should convert the response into a remission. Maintenance (or prophylactic) treatment should limit the recurrence of further episodes (usually after a remission of 4 to 9 months).

Despite a comprehensive series of reports documenting the efficacy, safety and tolerability of moclobemide as an antidepressant in acute depression there are relatively few published reports on the continuation and maintenance effects of this drug.

Continuation Treatment

In a six-month, open-label study of moclobemide-continuation treatment (300 to 450 mg) 6 of 81 patients (7.5%) relapsed, although another 10 patients (12%) were lost during follow-up (89). From this study a sustained efficacy across 6 months of continuation treatment was calculated to be at least 80.5%. Study completers had a further 40% reduction in HAM-D as compared to the acute phase therapy (89).

Lonnqvist et al. (152) studied continuation therapy in outpatients who responded to acute phase therapy (6 weeks) with either fluoxetine ($n = 30$) or moclobemide ($n = 29$). During the continuation phase of 12 weeks one (3%) patient and two (7%) patients relapsed in the fluoxetine and moclobemide groups, respectively. Using rigorous criteria for response (HAMD ≤ 7), the moclobemide group showed an increase in responses from 55 to 65% between week 6 and week 18, compared with an increase from 33 to 57% in the fluoxetine group. The differences were not statistically significant. The incidence of premature discontinuation was not significantly different in the two groups. The incidence of adverse events during continuation phase was reduced to one-third (152).

Lecrubier et al. (143) reported the results of continuation treatment following acute phase therapy (6 weeks). The rates of responders remained not significantly different at 6 and 12 weeks. Responders increased from 63% ($n = 57/90$) to 69% ($n = 44/64$) and from 65% ($n = 51/78$) to 80% ($n = 48/60$) in the moclobemide and clomipramine groups, respectively. The percentage of "very good" ratings for tolerability during the first 6 weeks of therapy was significantly higher in the moclobemide group (48 vs. 15.1%) and remained so for the continuation period (48.5 vs. 20.6%) (143).

Across these studies, continuation therapy with moclobemide was accompanied by sustained response rates (60 to 80%) that would be superior to those observed in placebo-controlled discontinuation designs (232).

Maintenance Treatment

In two case reports the initial favorable responses to moclobemide became blunted during the first year of treatment and could not be restored by dose adaptations (140,187).

In a follow-up study of 102 moclobemide responders for one year of maintenance treatment, efficacy and combined efficacy/tolerability were judged to be "good" or "very good" for 96 and 85% of patients, respectively (221).

Moll et al. (164) investigated the recurrence rates in 300 patients selected from a larger, open, long-term study on the basis of their favorable response (HAM-D > 50%) to moclobemide (164). The authors reported recurrence rates of 25, 14.8, and 12.2% for the first, second and third six-month periods of maintenance treatment, respectively (164). Although of limited value due to the lack of controlled conditions, these rates of recurrence are comparable to those reported for other antidepressants (121). In patients selected by Moll et al. HAM-D-decrease rates of 45 and 68% from the baseline at 2 and 12 months, respectively, were reported for moclobemide (164).

There is a lack of controlled trials addressing continuation and maintenance treatments involving classical or reversible MAO-inhibitors. However, there is limited but consistent evidence to suggest that these drugs have long-term efficacy in depressed patients and that treatment should be continued for 6 to 12 months at least in the case of refractory depression (121). Some evidence suggests that antidepressant therapy (including moclobemide) in combination with supportive psychotherapy might be superior to pharmacotherapy or psychotherapy alone (60).

Discontinuation Syndrome

No controlled dose reduction or discontinuation trial with moclobemide has been published in patients with depression (260). However, evaluation of a large safety database for panic disorder revealed that early withdrawal rates were similar (28%) for placebo ($n = 314$) and moclobemide ($n = 624$). It has been stated that no withdrawal syndromes have been reported after up to 3 years of treatment with moclobemide (136).

Refractory Depression

Even though there are many effective treatments for major depression, including psychotherapy and ECT, antidepressant therapy is considered the standard of care. Despite this emphasis on pharmacotherapy, 30 to 45% of depressed patients who are treated with antidepressants show only partial or no response (181). Refractory depression is generally defined as a depression that did not respond to the treatment with high doses of ≥2 classes of antidepressants.

Randomly assigning patients who have failed to respond to prior antidepressant treatment to placebo therapy is often perceived as unethical. Even controlled trials that do not involve placebo can present significant challenges to investigators. Clinicians tend to use two types of pharmacological strategies with patients who failed to respond to prior antidepressant treatment: augmentation and switching. Augmentation means that one drug enhances the effect of the other whereas switching involves the substitution of the failed agent with another, often one with a different mechanism of action (80,171).

The combination of moclobemide plus thioridazine was not superior to moclobemide plus placebo in 78 refractory patients. Either treatment was associated with response rates

of approximately 75% after 4 weeks of therapy (217). In a prospective open trial, 23 patients suffering from episodes of severe depression, which did not respond to at least two tricyclics or tetracyclics over several months, were augmented with 300 mg moclobemide. Within 4 weeks 13 patients (53.9%) responded as determined by a significant improvement in HAM-D (125). A few small open trials (usually of 4 to 6 weeks duration) reported response-rates of 55 to 75% after augmentation treatment of tricyclic- or SSRIs-resistant depression with 300 to 800 mg moclobemide (15,106,116). One study of moclobemide (329 ± 125 mg/d) plus a tricyclic (trimipramine: 117 ± 24 mg/d, doxepine 67 ± 24 mg/d or amitriptyline 94 ± 33 mg/d) recorded a response-rate of 70% in 18 hospitalized refractory patients (223).

Another trial enrolled patients with double depression, which had not responded to tricyclics and also to 6 weeks of treatment with fluvoxamine (77). Subsequently, one group was further treated with 300 mg fuvoxamine alone ($n = 18$) and the other group with 300 mg fluvoxamine and 600 mg moclobemide ($n = 18$). After 6 weeks, depression was significantly reduced in both groups: with a 20% decrease of depression in the fluvoxamine group and 40% in the combination group (difference not significant). In the latter group, two patients dropped out in week 3 due to excitation, insomnia and dysphoria (77). Although no serious drug interactions were reported in the above mentioned studies, it should be kept in mind that combining moclobemide with SSRI or clomipramine may increase the risk of serotonin syndrome (225). It is, therefore, generally recommended that second drugs should be started at low doses and titrated slowly and carefully and that patients should be monitored closely.

Depression in Elderly

Depression is common in the elderly but often remains unrecognized due to the masking of affective changes by somatic symptoms and cognitive deficits. The estimated prevalence of depression in people >65 years is about 10 to 15% (203).

The relatively benign side effect profile of moclobemide and its relatively low potential for adverse drug interactions, as well as the fact that the pharmacokinetics of moclobemide are age-independent (100,159), could offer special advantages in the treatment of elderly patients. Therefore, the antidepressant efficacy of moclobemide in elderly was tested in eight double-blind comparative trials (Table 5).

The 7-week study of Nair et al (169) included 109 patients and revealed moclobemide (400 mg) to be as effective as placebo, but significantly inferior to nortriptyline (50 to 170 mg). At the end of the treatment the remission rates in HAM-D were 11% (placebo), 23% (moclobemide) and 33% (nortriptyline). Anticholinergic and orthostatic events occurred more often in patients on nortriptyline than on moclobemide or placebo (169).

Roth et al. (201) performed a 6-week study of moclobemide (400 mg) vs. placebo in 694 patients suffering from major depression accompanied by dementia/cognitive decline. Moclobemide produced a significantly greater decline than placebo with a mean improvement of 51% in HAM-D score (201).

Altamura and Aguglia (3) compared moclobemide (400 mg) with fluoxetine (20 mg) in 68 patients. At the end of the 6-week treatment period, the mean reduction of HAM-D total score was 56 and 50% in patients treated with moclobemide and fluoxetine, respectively (not significant). Moclobemide was better tolerated than fluoxetine in terms of adverse gastrointestinal effects (3).

Bocksberger et al. (31) compared moclobemide (300 to 450 mg) with fluvoxamine (100 to 200 mg/d) in 40 patients for 4 weeks and found a more pronounced decline in the mean total score of MADRS in the moclobemide group than in the fluvoxamine group ($p = 0.009$). The CGI efficacy rating was "very good" or "good" in 84% in the moclobemide patients and 55% in the fluvoxamine patients. Tolerability was rated as "very good" or "good" in 100% of the moclobemide and 95% of the fluvoxamine-treated patients (31).

Burgarski-Kirola et al. (37) treated 42 inpatients with either fluoxetine (20 to 40 mg/d) or moclobemide (300 to 600 mg/d). Response rates were not significantly different between the groups: 74% (moclobemide) vs. 69% (fluoxetine). Moclobemide had a significantly faster onset of action that was evident during the second week of treatment (37).

Tiller et al. (233) compared moclobemide (150 to 600 mg/d) with mianserin (30 to 90 mg/d) in 20 patients with depression in an eight weeks long trial. The efficacy and tolerability of the two drugs was similar.

De Vanna et al. (62) described results of two multicenter trials. In the first trial, moclobemide (300 to 500 mg/d) was compared with mianserin (75 to 125 mg/d) in 80 de-

TABLE 5. Randomized double-blind comparative trials with moclobemide and placebo and/or antidepressant drugs in elderly patients with major depression*

Drugs Studies	Total number of patients (*N*)	Dosage of moclobemide (mg)	Duration of trials (weeks)	Overall efficacy[a]	ACE
Placebo (P)					
Roth et al. 1996	694[b]	400	6	M > P	M = P
Nortriptyline (N) 50–170 mg, Placebo (P)					
Nair et al. 1995	109	400	7	M = P	M = P > N
Imipramine (I) 75–100 mg					
Pancheri et al. 1994	30	400–600	8	M = I	M > I
Mianserin (MI) 30–125 mg					
Tiller et al. 1990	20	150–600	8	M = MI	M = MI
De Vanna et al. 1990	80	300–500	4	M = MI	M = MI
Maprotiline (MA) 75–150 mg					
De Vanna et al. 1990	39	150–300	6	M = MA	M = MA
Fluvoxamine (F) 100–200 mg					
Bocksberger et al. 1993	40	300–450	4	M = F	M = F
Fluoxetine (FL) 20–40 mg					
Altamura and Aguglia 1994 [abstract]	68	400	6	M = FL	M = FL
Bugarski-Kirola et al. 1996 [abstract]	42	300–600	6	M = FL	–

* >60 years old.

[a] Overall efficacy as derived from statistically significant differences between the groups with respect to primary efficacy criteria: ≥50% HAM-D-reduction and/or improvement of CGI and/or MADRS.

[b] Major depression (DSM-III) with dementia/cognitive decline.

Abbreviations: ACE, adverse clinical events; M, moclobemide; P, placebo; HAM-D, Hamilton depression rating scale; CGI, Clinical Global Impression (of efficacy); MADRS, Montgomery–Asberg depression rating scale.

pressed patients over a 4-week treatment period. At 4 weeks, the mean reduction in depression rating was 52% in either group. The overall tolerability was rated "very good" or "good" in 85% of patients of either group. In the second, 6-week-long trial, moclobemide (150 to 300 mg/d) was compared with maprotiline (75 to 150 mg/d) in 39 patients. The mean decline in depression rating was 85%, and tolerability was rated "very good" or "good" in ≥75% of patients of either group (62).

Pancheri et al. (183) compared moclobemide (400 to 600 mg) with imipramine (75 to 100 mg/d) over 8 weeks and found no significant difference between the mean HAM-D reduction in either group (183).

Amrein et al. (6) reported the results of Hoffmann-La Roche's data pool. Two hundred and twenty three elderly patients receiving moclobemide were available for comparison with 228 patients receiving tricyclics. Response rates for moclobemide were 50% based on HAM-D and 55% on the basis of CGI. These rates were similar to those obtained with tricyclics. Overall tolerability was rated "very good" or "good" in 85% of elderly patients on moclobemide compared with 68% on tricyclics (6). Additional data were available from 81 of the elderly patients on moclobemide and 82 patients on fluoxetine. The response rates to moclobemide in these patients were also similar to those obtained with fluoxetine (HAM-D: 47 vs. 49%, CGI: 49 vs. 51%) (6).

A recent meta-analysis confirmed that moclobemide is as potent as tri/heterocyclic antidepressants or SSRIs, also in elderly depressed patients (153).

ORGANIC DEPRESSION

Depression and Dementia

Cognitive disturbances emerging in the course of depression are generally resolved as depression declines. On the other hand, dementia is often accompanied by depression. A pathophysiological background may be given by a described loss of noradrenergic neurons mainly in the locus coeruleus of patients with Alzheimer's disease and coexisting depression (43). Reported prevalence rates of depression in Alzheimer's disease and vascular dementia range between 17 and 40% (7). As moclobemide was found to be devoid of anticholinergic and sedative effects in several performance tests (64,110,111,197) and may even improve disturbed cognitive function (2,8,79,183,255), it may be well suited for the treatment of elderly depressed patients with major cognitive deficits. This possibility was tested and two studies (183,201) support this assumption.

In a small study by Pancheri et al. (183), moclobemide ($n = 15$, up to 600 mg/d) was compared over 60 days with imipramine ($n = 15$, up to 100 mg/d). Moclobemide produced a mean reduction of HAM-D of 51% compared to 45% with imipramine. Either of the two drugs improved not only depression but also anxiety symptoms (HAM-A), with moclobemide showing a faster onset of action. In addition, moclobemide had an enhancing effect on cognition, which was not apparent with imipramine (Benton Visual Attention Test and the Digit Substitution Test of the Wechsler Adult Intelligence Scale). Tolerability results favored moclobemide over imipramine, particularly with respect to the anticholinergic side effects (183).

The second study, carried out by Roth et al. (201), was a large multicenter double-blind trial comparing moclobemide with placebo in elderly patients with cognitive decline and

depression. 694 patients were recruited with 511 meeting the criteria for major depression and dementia (DSM-III) while 183 met the criteria for major depression but not for dementia, although the latter patients suffered from cognitive decline. Patients from both groups were randomly allocated to the treatment with either moclobemide (400 mg/d) or placebo for 6 weeks. In both groups, depression symptoms improved steadily over time with the improvement being more pronounced with moclobemide than with placebo ($p < 0.001$). In the group of demented patients with depression, cognitive functions were improved over time with moclobemide as well as with placebo. However, the improvement was more pronounced with moclobemide (Mini-Mental state, Sandoz Clinical Assessment-Geriatric) (201). At the end of the double-blind phase, patients could enter open long-term treatment with moclobemide (300 to 600 mg/d). In total, 189 patients entered this open treatment including 109 patients treated with placebo during the double-blind period (7). The patients not responding to placebo revealed a clear-cut effect when switched to the open moclobemide treatment. After 6 weeks of open treatment, the mean HAM-D was reduced from 20 to 13. When continuing the open treatment the HAM-D score further decreased and reached normal values after open moclobemide treatment for 230 days (7). Moclobemide was well tolerated during this open extension phase with 22% of patients revealing adverse clinical events. Adverse events most frequently reported were dizziness (5.3%), insomnia (4.8%), and restlessness (4.2%) (7).

Barak et al. (16) described moclobemide (150 mg/d) to be beneficial in the treatment of depression in a 76-year-old patient with vascular dementia.

Post-Stroke Depression

Depression is also present in 25 to 30% of stroke patients. Due to its preclinical neuroprotective potential, moclobemide has been considered to be the antidepressant of choice for post-stroke depression (234). However, no clinical trials that can address this issue have been published.

Depression and Multiple Sclerosis

Depression is common also in patients with multiple sclerosis (MS), but tricyclic antidepressants have not been well tolerated by patients with MS. In an open 3-month trial, 9 out of 10 MS-patients treated with moclobemide (150 to 400 mg/kg/d) had complete remission of their depression. Four patients reported side effects including nausea and insomnia, but the authors concluded that moclobemide was well tolerated (17).

Depression Following Traumatic Brain Injury

Major depression following traumatic brain injury is a common phenomenon. One open study (174) investigated moclobemide's effect in 26 patients suffering from major depression of late onset (mean 4.67 years after traumatic brain injury). Twenty three patients receiving moclobemide (450 to 600 mg/d) responded to the drug. The onset of action of moclobemide was described as surprisingly rapid with the majority of patients responding by day 3 of therapy (174).

OTHER INDICATIONS

Social Phobia

Social phobia has been reported to be the third most frequently occurring psychiatric disorder after major depression and alcohol dependence in a population survey (123). It has an early age of onset, is chronic and generally unremitting (177). It is also described to be associated with a high lifetime risk of psychiatric comorbidity (mainly major depression, alcohol dependence and other anxiety disorders) (167). The efficacy of phenelzine and tranylcypromine has been confirmed in several controlled trials (93,145,146, 244). Moclobemide has been studied in the treatment of social phobia in one open trial (28), four placebo-controlled trials (113,176,204,247) (Table 6) and one open long-term study (250). All controlled trials underwent a single-blind placebo-phase to exclude placebo-responders. Responders were identified by several rating-scales with Liebowitz Social Phobia Scale (145,146) and CGI (101) as primary efficacy markers. Patients suffering from major depression, substance abuse, psychotic disorders and other anxiety disorders were not included in the controlled studies.

Versiani et al. (247) using a flexible-dose regimen compared moclobemide (up to 600 mg), phenelzine (up to 90 mg) and placebo in 78 Brazilian patients. After 8 and 16 weeks of randomized treatment, moclobemide was found to be significantly more efficacious than placebo but not different from phenelzine. Phenelzine was found to be superior to placebo earlier than moclobemide (at week 4). By week 16, 91% of patients on phenelzine were "almost asymptomatic" vs. 82% on moclobemide. Moclobemide was much better tolerated than phenelzine. Patients, who were gradually withdrawn from active drugs relapsed by week 24 (247).

TABLE 6. Randomized double-blind trials with moclobemide in patients with social phobia

Drug Study	Total number of patients (*N*)	Dosage of moclobemide (mg)	Duration of trials (weeks)	Overall efficacy[a]	Overall tolerability[b]
Placebo (P)					
IMMS 1997	578	300	8	M = P	M = P
		600	12	M > P	M = P
Noyes et al. 1997	506	75/150/300/600/900	12	M = P	M = P
Schneier et al. 1998	77	728	8	M = P	M = P
Phenelzine (PH) 68 mg, Placebo (P)					
Versiani et al. 1992	78	580	16	M = PH > P	M = P > PH

[a] Overall efficacy as derived from statistically significant differences between the groups with respect to improvements of Liebowitz Social Phobia Scale and CGI for efficacy at least.
[b] Overall tolerability as derived from statistically significant differences between the groups with respect to amounts of adverse clinical events and deteriorations of CGI for tolerability
Abbreviations: M, moclobemide; IMMS, International Multicenter Trial Group on Moclobemide in Social Phobia.

The International Multicenter Trial Group on Moclobemide in Social Phobia (113) compared moclobemide 300 mg/d, 600 mg/d, and placebo in 578 patients. The 600-mg group was significantly superior to the placebo-group at week 8 and week 12 in contrast to the 300-mg group. However, the magnitude of the drug effect was considerably smaller than that found by Versiani et al. (247), with CGI-response rates (much or very much improved) of 47, 41, and 34% for 600 mg, 300 mg of moclobemide, and placebo, respectively (113).

Another large multicenter study by Noyes et al. (176) was carried out on 506 patients in the United States to determine the efficacy and safety of 5 doses of moclobemide compared with placebo. The doses investigated were 75, 150, 300, 600, and 900 mg. However, with only 82 to 86 patients per treatment group, the study had little power to demonstrate significant differences between the dosage groups. No significant difference in response rates to placebo and various doses of moclobemide was observed at week 12, although the 900-mg group revealed a more intensive decline in the Liebowitz Social Phobia Scale. This may point to a better response with higher doses of moclobemide. Moclobemide was well tolerated. A significant minority of subjects reported insomnia as an adverse event on higher doses of moclobemide (176).

Schneier et al. (204) investigated moclobemide (up to 800 mg/d) in a flexible-dose regime in 77 patients. By week-8 intention-to-treat analysis, 17.5% (7/40) on moclobemide and 13.5% (5/37) on placebo had responded. Furthermore, moclobemide was found to be not significantly superior to placebo in 8 out of 10 primary outcome measures pointing to the absence of overall efficacy of moclobemide in the treatment of social phobia. Adverse effects on moclobemide were not significantly different from those of placebo (204).

In a follow-up study lasting 2 years, Versiani et al. (250) treated 93 patients suffering from relatively severe social phobia with moclobemide (mean daily dose of 712 ± 75 mg). The drug was discontinued in 59 patients, who had responded initially, for at least one month. Relapses were observed in all but 9 subjects. Renewal of treatment with moclobemide produced a slow improvement taking 6 months to reach optimal response (Fig. 2A). Outcome was positively related to the severity of social phobia and negatively related to concomitant generalized anxiety and dysthymia. The strongest predictor of poor response was comorbidity with alcohol misuse. Tolerability was evaluated in all recruited patients. All adverse events were mild with most being transient and none causing premature discontinuation. The most frequent adverse events reported were nausea, headache and insomnia. Adverse events were observed early in the treatment phase (Fig. 2B). Overall, 10% of patients reported at least one adverse event at each monthly visit (250).

Taken together, there exists some, although less robust, evidence that moclobemide is efficacious and well tolerated in social phobia (at doses about 600 mg/d). The long-term study (250) showed that response in social phobia is gradual and may take time to evolve fully, subsequently persisting with treatment. Based on these findings it has been proposed that treatment should be continued for approximately 6 symptom-free months before tapering, and the medication should be reintroduced if symptoms recur (250). Moclobemide might be more beneficial in combination with established behavioral or cognitive-behavioral therapies (18,262).

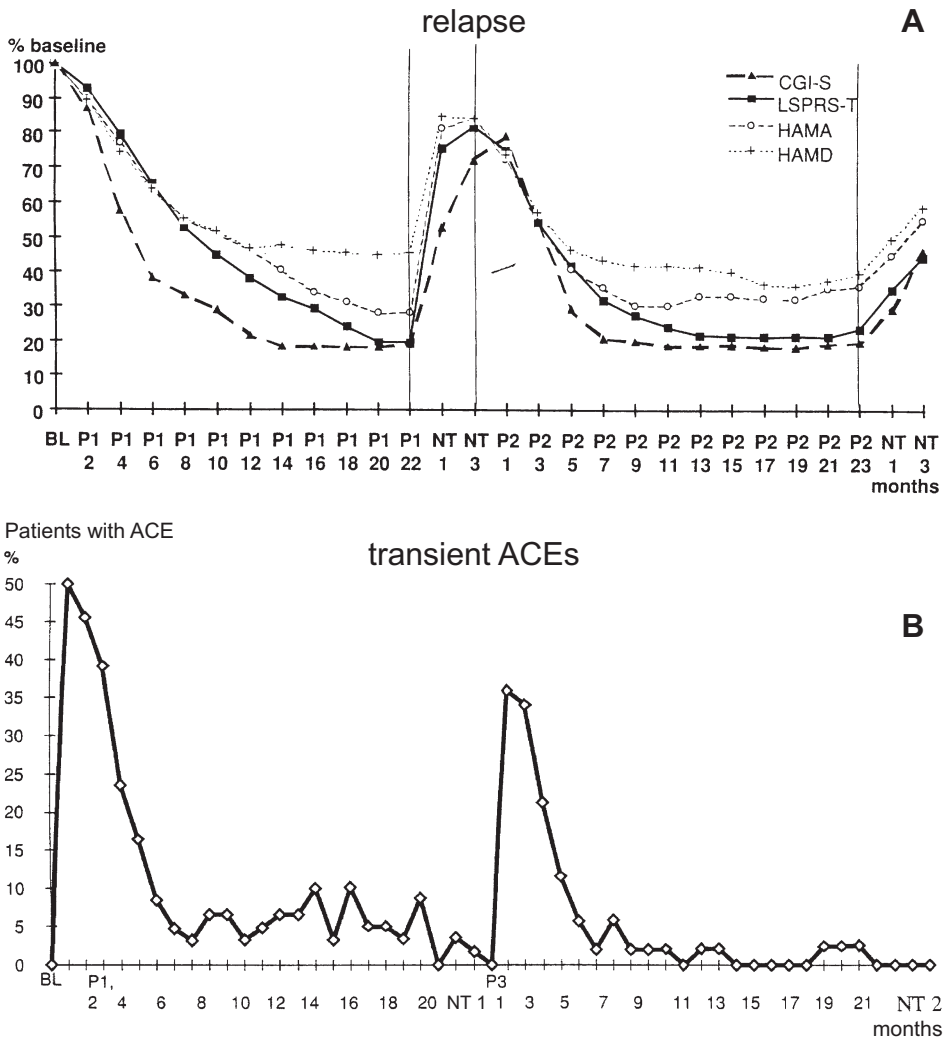

Fig. 2. A: Relapse after gradual discontinuation of long-term treatment with moclobemide. Clinical Global Impression of Severity (CGI-S, Liebowitz-Social-Anxiety-Scale Total (LSAS-T), Hamilton Anxiety (HAM-A) and Depression (HAM-D) rating scale scores in the two moclobemide treatment phases (P1 and P2) and during no treatment phases (NT), $n = 59$. B: Time course of adverse clinical events (ACE), all were considered to be mild and mostly transient; BL, baseline. Reproduced with permission from ref. 250.

Panic Disorder

Irreversible monoamine oxidase inhibitors, especially phenelzine, have been the pharmacotherapeutic "gold standard" for the treatment of panic disorder for many years (239a). Tricyclics and SSRIs (13,186) have recently replaced them. Three controlled studies have been published which tested the efficacy of moclobemide in panic disorder with or without agoraphobia (132,149,236,237). Among them are two which compare moclobemide with fluoxetine (236,237) or clomipramine (132). Though SSRIs and clom-

ipramine have been shown to be superior to placebo in limiting panic attacks (13,186), sufficient placebo-controlled studies with moclobemide are still lacking.

One recent study compared combinations of cognitive-behavioral therapy (CBT), clinical management (CM, regarded as "psychological placebo"), moclobemide and placebo in 55 patients suffering from panic disorder with agoraphobia (149). By week 8, both combinations, moclobemide/CM and placebo/CM, were significantly inferior to moclobemide/CBT or placebo/CBT in limiting panic attacks and agoraphobia. In other words, moclobemide (with "psychological placebo") was not superior to placebo (with "psychological placebo") and significantly inferior to CBT (149).

The studies comparing moclobemide with fluoxetine (236,237) or clomipramine (132) revealed that moclobemide was as efficacious as each comparison drug in blocking panic attacks. At the end of week 8, 49% of patients treated with moclobemide (n = 67, 450 mg) and 53% of patients treated with clomipramine (n = 68,150 mg) were panic free (132). Another study revealed that 63 and 70% of patients were without panic attacks after 8 weeks of treatment with moclobemide (n = 182, 498 ± 68 mg) and fluoxetine (n = 184, 20.5 ± 2.7 mg), respectively (236,237). At one year, for those on continuation treatment, 97% on moclobemide (n = 61) and 100% on fluoxetine (n = 65) remained much improved or better in CGI (237).

All comparisons reported a high incidence of adverse clinical events, which may reflect the patient population, as the rates were similar to those reported in placebo-controlled studies of panic disorder (190a,236,237). Tolerability of moclobemide was rated to be superior to clomipramine and similar to fluoxetine (132,237).

Sexual Function

One case report described a female suffering from major depression developing hyperorgasmia but no other signs of hypomania on moclobemide. This symptom disappeared after switching to doxepine (138). Additionally, three cases of moclobemide-induced hypersexuality in patients with stroke or Parkinson's disease were reported (130). Studies on healthy volunteers (122) and patients with depression (189,198) indicated that moclobemide (300 to 600 mg/d) did not induce significant changes in sexual desire and function.

It was striking that, in contrast to tricyclics and SSRIs, adverse effects with moclobemide did not include sexual dysfunction (166,189,190). On the contrary, in depressed patients moclobemide was more likely to produce an improvement in libido, impaired erection/ejaculation or orgasm than doxepine. There was, however, no significant difference in the antidepressant efficacy of the two drugs (189). A recent large comparative trial on 268 depressed adults over a period of 6 months revealed sexual dysfunction among reported adverse events in 21.6 and 1.9% of the patients treated with SSRIs and moclobemide, respectively, while the antidepressant efficacy of both drugs was similar (190). A large prospective study in Spain involving 1022 outpatients listed the incidence of sexual dysfunction for various antidepressants as follows: SSRIs (57 to 72%), venlafaxine (67%), mirtazapine (24%), nefazodone (8%), and moclobemide (4%) (166).

Fluoxetine-induced sexual impairment was reversed in 5 patients when they were switched to moclobemide (196). It was proposed that moclobemide should be the antidepressant of choice for patients with sexual dysfunction or for those who consider normal sexual function very important (190).

In a recent controlled 8-week trial, 12 male outpatients suffering from psychogenic erectile dysfunction and without any other neuropsychiatric condition were treated with moclobemide (450 to 600 mg/d) (157). The CGI-scale revealed a markedly strong improvement with moclobemide as compared to placebo. However, as previously reported (222), the nocturnal penile tumescence was not altered by moclobemide (157).

Parkinson's Disease

It is recognized that depression is the most psychopathological finding in Parkinson's Disease (PD). Antidepressant efficacy of moclobemide in PD has been reported (229). In a recent open label study on 10 patients with idiopathic PD and a 3 to 15 months lasting depressive episode a combined treatment with moclobemide (600 mg) and selegiline (20 mg) was superior to moclobemide (600 mg) alone in limiting depression (115). However, the selegiline dose was low and the clinical relevance of this study is not clear. A slight but significant improvement of cognitive performance was observed during the combined therapy. The study was conducted over a 6-week period with strict dietary tyramine restrictions and typical anti-parkinsonian medication. No elevation of blood pressure was observed and in both groups one patient developed symptomatic hypotension (115). Small open studies found an improvement in levodopa-induced dyskinesias by moclobemide. At 300 to 450 mg moclobemide significantly shortened the duration of "off" times without improving "on" times (202,207,226). A slight worsening of levodopa-induced dyskinesia was also described (226). However, it was suggested that moclobemide should be indicated in elderly or depressed fluctuating PD patients (226).

Epileptic Disorders

Proconvulsant activity, mostly associated with amoxapine, maprotiline, trazodone, mianserin, bupropion, and most tricyclics, has not been observed with moclobemide (4,213,259). However, at extremely high doses moclobemide may occasionally produce convulsions possibly due to a serotonergic reaction (45). Hilton et al. analyzed data from Roche Drug Safety and found that the incidence of reported convulsions in patients receiving moclobemide was lower than expected from the background incidence rate in the general population (109). Animal pharmacology suggests that moclobemide has some anticonvulsant activity (32,96,213). Nevertheless, lack of clinical experience in epileptic patients with affective disorders and probable interactions with anticonvulsants which are metabolized by CYP1A2, CYP2D6, or CYP2C19 restrict the use of moclobemide in patients suffering from epileptic disorders (50).

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD occurs in 3 to 10% of school age children and is one of the most common psychiatric disorders in the childhood and adolescence. The cause of ADHD is unknown, but attempts were made to correlate ADHD with MAO activity. An age-related decrease in thrombocytic MAO-activity does not occur in children with ADHD (258). In a small trial, moclobemide (150 mg/d) was given to 12 children with ADHD over a period of 4 weeks (239). Moclobemide increased concentration and attention, in children, but mood changes and explosive behavior continued to be present, though on a lower level. Parents rated a 40% improvement of their children's behavior (239). Furthermore, combined treatment of

moclobemide (600 mg/d) and methylphenidate (10 mg/d) was reported to be beneficial in the treatment of a 22-year-old man suffering from comorbid depression and adult ADHD (168).

Miscellaneous Disorders

In two cases combination of moclobemide (3 × 150 mg) and tyramine-containing Bovril® (3 × 12 g) enhanced hypotension induced by clozapine (231) or central autonomic failure (120). One letter and one retrospective study on 44 patients described a beneficial effect of 300 to 450 mg moclobemide in the prophylactic treatment of migraine with a more marked effect in the migraine with aura (47,161). One letter reported an improvement of Kleine–Levin syndrome with 300 mg moclobemide (44). Another open study described a beneficial effect of moclobemide in the treatment of posttraumatic stress disorder (170). A further controlled trial revealed that moclobemide (450 to 600 mg/d) might not be helpful in patients suffering from fibromyalgia, who were free from clinically relevant psychiatric problems (105). At 600 mg/d moclobemide was not different from placebo in reducing binge eating episodes in 52 females suffering from bulimia nervosa (40). One case report described that symptoms of tardive akathisia disappeared after 20 days of treatment with 600 mg moclobemide (76). Furthermore, moclobemide (450 mg/d) was reported to ameliorate negative, depressive and general symptoms in 11 chronic schizophrenic patients after a treatment period of 8 weeks (208). Moclobemide (200 to 400 mg/d for 8 weeks) facilitated smoking cessation in one placebo-controlled trial involving 88 heavy smokers (27).

TOLERABILITY AND SAFETY

A database of several thousand patients treated with moclobemide has been published (6). According to data available from the manufacturer to the end of June 1993, adverse clinical effects (ACEs) have been reported in less than 0.2% of approximately 780,000 subjects exposed (109). In general practice, however, ACE-rates of up to 50% have been reported. These ACEs were mild and transient in most cases (109,235).

Comparison with Placebo

In studies comparing moclobemide ($n = 1291$) with placebo ($n = 810$) headache (11.3%), dry mouth (10.3%), and "excitatory" events (12.2%), such as agitation, anxiety, excitability, restlessness, panic and hypomania, were the most commonly reported ACEs (45). However, the frequency of these events did not significantly differ from that in placebo-treated patients (45). ACEs that occurred significantly more frequently in moclobemide than in placebo-treated patients were dizziness (7.9 vs. 5.4%), nausea (7.2 vs. 3.8%) and insomnia (7.2 vs. 4.4%) (45). Similar results were found in a previous analysis of 2203 depressed patients (163). In a separate report covering a large overlapping database, only one hypertensive crisis was described during moclobemide (246). An incidence of less than 0.1% was suggested (246). In 624 patients suffering from panic disorder, two ACEs on moclobemide (insomnia and dizziness) significantly exceeded the ACE-rate for

placebo. The ACE-rates for headache and nausea were lower for moclobemide than for placebo in this trial. Moclobemide had no significant effect on blood pressure (236).

In 60 healthy volunteers, treated either with moclobemide (300 mg/d) or placebo for 3 weeks there was no significant difference in the ACE rates between the two treatment groups (56). This trial also elucidated the strong role of personality factors, such as neurotic and hypochondriac attitudes, in reporting an ACE. In both groups, nearly 60% reported ACEs, including headache, tiredness and sleep disturbance. (56). It has been recently described that the most active drug ACEs and some placebo-subtracted ACEs were significantly correlated with placebo ACEs suggesting a relationship with non-pharmacological heterogeneity (251).

Comparison with Tricyclic and Heterocyclic Antidepressants

Comparing 1288 patients on tricyclics with 1291 patients on moclobemide, Chen and Ruch (45) described that moclobemide-therapy was associated with a negligible incidence of anticholinergic and antihistaminergic side effects, such as dry mouth, sweating, tremor, somnolence, dizziness, blurred vision, and sexual dysfunction. However, moclobemide therapy resulted in significantly more complaints of headaches and insomnia than tricyclics. Discontinuation of therapy due to ACE tended to be less frequent in patients treated with moclobemide (2 to 13%) compared to patients treated with tricyclics (5 to 30%) (85).

Anticholinergic ACE were much more frequently reported in patients treated with mianserin or maprotiline than moclobemide (38,62,88,139,224,243). It was stated that moclobemide as well as maprotiline were safe with respect to their cardiovascular effects (ECG, blood pressure, heart rate) (88,109,224).

Comparison with SSRIs

In two trials, moclobemide was better tolerated than fluvoxamine (19) or fluoxetine (134). All other published comparisons described no significant differences in the overall tolerability of moclobemide and SSRIs (Table 2). However, their individual ACE-profiles are somewhat different. In the largest trials the following ACEs were found to be significantly more frequent with SSRIs: nausea (fluoxetine) (150), dry mouth and other anticholinergic ACEs, nausea (fluvoxamine) (36), headache, blurred vision (fluoxetine) (134), sedation, nausea, vomiting (fluoxetine) (257), and sexual dysfunction (fluoxetine) (198). In the moclobemide-treated patients dry mouth (134) and insomnia occurred more often (257). Phillip et al. (190) investigated the ACEs in 268 depressed patients treated with moclobemide or fluoxetine. Sexual dysfunction was ten times more frequent in patients receiving fluoxetine.

Long-Term Treatment

In 1120 patients who received moclobemide for a longer period of time (>44 days), the most common ACEs were insomnia, nausea, dizziness, dry mouth, epigastric discomfort, tachycardia and palpitations. They occurred in 2 to 5% of the patients (164). There were no relevant changes in blood pressure, even during treatment periods in excess of one year. When values at the end of the treatment period were compared with the baseline

before treatment only mean heart rate was slightly decreased. There was no change in the mean bodyweight or in the laboratory parameters (alkaline phosphatase, bilirubin, γ-GT, GOT, GPT, hemoglobin, leucocytes) (164).

Treatment of Elderly

The database of the manufacturer in June 1995 comprised comparative data from elderly patients (>60 years) treated with moclobemide ($n = 1054$), placebo ($n = 483$), tricyclics ($n = 480$), or SSRIs ($n = 134$). There were no ACEs in 62.7% of patients on placebo and 59.6% of patients on moclobemide. The incidence of ACEs in patients on moclobemide and placebo is shown in Table 7. There was no statistically significant difference in the frequency of ACEs in different treatment groups (6).

The comparison of the effects of tricyclics with those of moclobemide revealed that insomnia was significantly more frequent in patients on moclobemide than on tricyclics. Anticholinergic ACEs (dry mouth, constipation, tremor, sweating) as well as sleepiness and daytime tiredness occurred significantly more frequently on tricyclics. Headache, nausea and dizziness were found with a similar frequency in either treatment group (6).

In patients treated with SSRIs, five ACEs (nausea, headache, nervousness, dry mouth, and insomnia) occurred with a frequency of ≥5%. In patients treated with moclobemide, headache and nervousness were the most frequent ACEs reported. These ACEs were similar to those observed with SSRIs. Moclobemide as well as SSRIs were claimed to be well-tolerated (6).

In the long-term treatment (over 6 months) trial involving 566 elderly patients with depression 2 out of 3 patients receiving moclobemide were completely free of any ACEs. The ACEs-profile in the long-term treatment trial was similar to that in short-term treatment, but the frequency of ACEs was lower (6). No negative cognitive effects have been reported in the elderly. It has been suggested that moclobemide may have a favorable effect on cognitive function (2,8,79,183,255), although this effect may be secondary to its antidepressant effect.

TABLE 7. Adverse clinical effects (ACEs) reported in % of elderly patients

ACE	Moclobemide ($N = 502$)	Placebo ($N = 483$)
Dry mouth	7.4	6.0
Sleep disturbance	8.4	6.2
Headache	8.4	11.4
Nausea	5.6	3.5
Dizziness	5.4	4.3
Constipation	4.4	3.1
Tremor	1.4	1.2
Agitation, nervousness	10.4	10.8
Sleepiness, tiredness	5.0	6.2
Sweating	0.6	1.2
None	59.6	62.7

* Reported in double-blind, 6-week trials of moclobemide vs. placebo. Adapted from ref. 6.

Cardiovascular Safety and Blood Pressure Changes

In the analysis of large prospective studies involving a total of 13741 patients treated with moclobemide hypertension or hypotension occurred in 0.11 and 0.04% of the patients, respectively (59). Another analysis involving 11569 patients treated with moclobemide revealed hypertension in 0.05% of the patients (48). In still another long-term study that included a total of 1120 patients no consistent changes in the supine or standing blood pressure were detected. (164). Also, in patients with pre-existing hypertension no significant increases beyond baseline values were observed (164). The experimental data with moclobemide suggest that its effects on cardiovascular reflexes are negligible (49). One case of peripheral edema related to moclobemide treatment has been reported (1).

Hepatobiliary Safety

Moclobemide's ACE-profile does not suggest an increased risk of hepatobiliary disorders (109,148). However, one case of fatal intrahepatic cholestasis related to the use of moclobemide has been reported (238) and was interpreted as induced by an idiosyncratic reaction to moclobemide (71).

Pregnancy

In pregnancy, as with all drugs, moclobemide should be avoided if at all possible. If its use is essential, the prescription of moclobemide should be restricted to the last trimester. One female with chronic dysthymia used moclobemide (300 mg/d) throughout her first pregnancy (195). The course of pregnancy was healthy and natural delivery was uneventful. The psychomotoric and somatic development of the child within the first 14 months of life was normal (195).

Dependence

Classical MAO inhibitors, such as tranylcypromine and phenelzine, have been described to have some potential for abuse (20,242). To date, similar findings have not been reported for moclobemide.

Suicidal Behavior

An increased risk of suicidal behavior described in the DUAG-study (51), has not been confirmed (109). An analysis of suicide mortality on antidepressants in Finland from 1990 to 1995 revealed that moclobemide is as safe as SSRIs or mianserin (179).

Overdose and Fatalities

Intoxications with moclobemide have been reported in over 40 published cases (85, 235). At extremely high doses (about 20 g) moclobemide did not cause fatalities (45,108, 109,114), except in one possible case in which postmortem blood concentration of moclobemide was 137 mg/L (39). Chen and Ruch (45) reported a female who developed con-

vulsions, hyperthermia and tachycardia after ingestion of 10g moclobemide. The plasma concentration of moclobemide in this case was 36.5 mg/L measured at 6 h after the overdose (45). Ingestion of up to 2 g moclobemide resulted in, if any, only mild gastrointestinal symptoms. Mild disorientation, drowsiness, agitation, tachycardia and increased blood pressure were reported to be caused by moclobemide at the dose range of 3 to 8 g. These symptoms were reversible without any organic sequelae (85,114). Thus, moclobemide is regarded to be relatively safe, when taken alone, even in overdose (85,102).

In the past seven years, 12 fatalities have been reported following coingestion of an overdose of moclobemide and a SSRI or clomipramine (52,81,156,172,191,200,212). In most cases, death was attributed to the serotonin syndrome (225).

Serotonin Syndrome

Serotonergic drugs are sometimes associated with a potentially lethal hyperserotonergic, hypermetabolic state of the CNS. This so-called "serotonin syndrome" is comprised of confusion, slurring of speech, hypomania, restlessness, hyperthermia, shivering, tachycardia, labile blood pressure, diaphoresis, diarrhea, muscular rigidity, hyperreflexia, myoclonus, tremor, convulsions and, finally, cardiac arrest and multiple organ failure (225).

Two elderly patients and one adolescent were reported to have developed a non-fatal serotonin syndrome with the therapeutic doses of moclobemide alone (82,178).

Other cases of non-fatal serotonin syndrome have been caused by combined overdoses of moclobemide and serotonergic drugs, such as SSRIs, clomipramine or venlafaxine (25,92,166,211,214). Gaudins et al. (92) described two patients who developed a serotonin syndrome while on therapeutic doses of moclobemide and paroxetine. The syndrome improved with cyproheptadine (4 to 8 mg p.o.), a non-specific serotonin receptor antagonist. Furthermore, in one patient the syndrome developed immediately after a switch from fluoxetine to moclobemide (57). In an open trial involving 50 patients serotonin syndrome developed in one patient who received combined therapy with moclobemide and a SSRI (106). One possible serotonin syndrome has been described in a patient on combined therapy with moclobemide and pethidine (95).

Interaction Profile

Since moclobemide has a relatively low protein-bound interference with the absorption or competition for plasma proteins, its protein binding should be negligible. However, as a substrate for CYP2C19, moclobemide undergoes extensive hepatic metabolism (97). Other cytochrome P450-isoenzymes, such as CYP1A2 and CYP2D6, were found to play a negligible role in the metabolism of moclobemide (103,159). A pharmacokinetic interaction of moclobemide and cimetidine has been described. In cimetidine-treated patients moclobemide clearance is reduced (206), so that the dose of moclobemide should be reduced by 50% (5). On the other hand, moclobemide inhibits CYP2C19 and to a lesser extent CYP1A2 and CYP2D6 (21,97). Therefore, theoretically moclobemide could elevate plasma levels of antidepressants, antipsychotics, β-adrenoreceptor antagonists, opioids, anticoagulants and other drugs (Table 8) (74,162,192).

Only in a few clinical studies pharmacokinetic interactions of moclobemide with other antidepressants have been described. König et al. (126) found in an open pilot study of

therapy-resistant depressive inpatients a significant increase in the plasma level of trimipramine (39%). Wallnöfer et al. (253) described that in healthy volunteers fluvoxamine plasma concentrations remained unchanged during co-administration of moclobemide over a period of 4 days, while plasma concentrations of moclobemide were slightly increased (253). Dingemanse et al. (69) described that in healthy volunteers multiple dose treatment with moclobemide did not affect plasma levels of fluoxetine or norfluoxetine. These authors found also that fluoxetine inhibits the conversion of moclobremide to its lactam metabolite (Ro 12-8095) but not to the N-oxide metabolite (Ro 12-5637) (69).

Some human pharmacodynamic interaction studies provided information on the combined therapy with moclobemide and sympathomimetic drugs (ephedrine, tyramine), antiparkinsonian drugs (levodopa+benserazide, entacapone, selegiline), antimigraine agents (sumatriptan, almotriptan), an I_1-imidazoline-receptor ligand (moxonidine) and SSRIs.

In respect to possible interactions with MAO inhibitors, tyramine is the most extensively investigated indirect sympathomimetic compound. It has been shown that moclobemide significantly potentiates the tyramine pressor response (by a factor of 2 to 4) (128). However, this interaction is not likely to be of clinical relevance, since relatively large amounts of tyramine would have to be ingested to induce clinically relevant increases in blood pressure (33). In spite of this, moclobemide at larger doses (above 900 mg/d) has been associated with a relevant risk of hypertension during tyramine ingestion (68). The concomitant use of other indirectly acting sympathomimetics, such as phenylephrine (i.v.)

*TABLE 8. Common examples of substrates of cytochrome P450 isoenzymes which can be inhibited by moclobemide**

CYP1A2	
Substrates:	R-warfarin, caffeine, propranolol, paracetamol, theophylline, verapamil, methadone, phenacin, tacrine, clozapine, haloperidol, amitriptyline, clomipramine, imipramine, trimipramine, trazodone
Inhibitors:	ciprofloxacin, erythromycin, fluvoxamine, paroxetine
Inducers:	smoking cigarettes, phenytoin, phenobarbital, omeprazole
CYP2C19	
Substrates:	S-warfarin, hexobarbital, cimetidine, diazepam, omeprazole, phenytoin, propranolol, amitriptyline, citalopram, clomipramine, imipramine
Inhibitors:	cimetidine, ketoconazole, omeprazole, fluoxetine, fluvoxamine, tranylcypromine
Inducer:	rifampicin
CYP2D6	
Substrates:	encainide, flecainide, mexiletine, propafenone, alprenolol, bufarolol, metoprolol, propranolol, timolol, 4-hydroxyamphetamine, debrisoquin, perhexiline, phenformin, sparteine, codeine, methadone, dextromethorphane, ethylmorphine, haloperidol, clozapine, perphenazine, risperidone, thioridazine, fluoxetine, N-desmethylcitalopram, paroxetine, mianserin, amitriptyline, clomipramine, N-methylclomipramine, desipramine, imipramine, nortriptyline, trimipramine, venlafaxine, mCPP metabolite of nefazodone, and trazodone
Inhibitors:	quinidine, fluphenazine, haloperidol, thioridazine, fluoxetine, norfluoxetine, paroxetine, amitriptyline, desipramine, clomipramine

* Moclobemide itself is a substrate of CYP2C19; after (74,162,192).

or ephedrine (p.o.), was accompanied by a potentiation of an amine-induced increase in blood pressure to about a similar extent as with oral tyramine (65,261). Palpitations and lightheadedness were the most frequently reported adverse events (65).

Co-administration of moclobemide with the MAO-B inhibitor, selegiline, has been associated with a supra-additive tyramine potentiation (67,129). Therefore, a combination of these two drugs requires strict dietary restrictions of tyramine. Theoretically, the risk for a serotonin syndrome should be increased on this drug combination (158). However, no serious adverse events have been reported in studies with healthy volunteers without tyramine-restriction (65,67,129) and in one small study in patients with Parkinson's disease under tyramine restriction (115). Concomitant treatment of healthy volunteers with moclobemide and Madopar® (levodopa + benserazide) was described as being well tolerated with an increase in dopamine-type adverse events like nausea and vomiting (65). However, this small study was clearly limited by low doses of Madopar® (up to 250 mg/d). Another trial on healthy subjects revealed no changes in heart rate, blood pressure or other measured hemodynamic parameters during a combination therapy with moclobemide (150 mg) and the COMT-inhibitor entacapone (200 mg) (112).

The combination of moclobemide with the antihypertensive agent moxonidine was investigated with respect to potential cognitive disturbances in healthy volunteers and found to be safe (256).

As outlined above the combination of moclobemide with serotonergic drugs should be used with caution because of the risk of a potential serotonin syndrome. In contrast to moclobemide's combination with SSRI and clomipramine, no serious adverse events have been reported with the concomitant use of carbamazepine or lithium to date (5,210,235). Data available from 50 patients receiving moclobemide (150 to 675 mg/d) and lithium for a period of 3 to 52 weeks indicate no evidence of an apparent clinical interaction (5).

MAO-A is involved in the metabolism of triptans, which stimulate various 5-HT_1 receptors (70, 75). In fact, co-administration of oral triptans with MAO-inhibitors is contraindicated in current product labeling (160). A small observation study with healthy volunteers (30) and a careful literature search (90) found no evidence for clinically relevant adverse consequences of the combined use of sumatriptan and moclobemide. Recently, moclobemide was described as increasing plasma concentrations of almotriptan. Almotriptan is a new 5-$HT_{1B/1D}$ agonist, used in the treatment of acute migraine. Moclobemide increased plasma concentrations of almotriptan in healthy volunteers by ca. 37% without any cardiovascular side effects (84).

Severe interactions have been reported between traditional MAO inhibitors and opioids, such as pethidine and dextromethorphan (5,218). On the other hand, morphine as well as fentanyl have been used safely together with traditional MAO inhibitors (155). Animal data indicate a possibility of a strong augmentation of the effects of pethidine and dextropropoxyphene by moclobemide (5). Therefore, the combination of moclobemide with either of these two drugs should be avoided (95). Data are available on 3 patients receiving moclobemide together with either codeine or dextropropoxyphene. One patient developed agitation, but it was not clear which drug elicited this response (5). It is recommended that the combined use of moclobemide and opioids should be undertaken very carefully until a larger database is available (5).

Data from clinical studies revealed no clinically relevant interactions of moclobemide with digoxin, oral contraceptives, glibenclamide, ibuprofen, nifedipine, hydrochlorothi-

azide, benzodiazepines, or neuroleptics (5,99,235,261). However, hypotension, tachycardia, somnolence, tremor and constipation were reported to be somewhat more frequent with moclobemide in combination with low potency neuroleptics than with moclobemide alone (5). A slightly enhanced hypotensive action was seen with metoprolol when used in conjunction with moclobemide (5). Subjects taking clomipramine had significantly more adverse effects after alcohol than subjects taking moclobemide (26). This may reflect data from animal experiments suggesting a negligible interaction between moclobemide and alcohol (241).

In healthy volunteers a switch from tricyclic antidepressants (amitriptyline or clomipramine) to moclobemide has been safely accomplished. (66). A large survey did not find any risk of a serotonin syndrome after switching from fluoxetine to moclobemide (235), although Delini-Stula et al. reported one case of serotonin syndrome under similar circumstances (57).

A few studies focused on the potential risk of an emerging serotonin syndrome during combined moclobemide + SSRI treatment. Two studies were published with a total of 43 healthy volunteers receiving moclobemide (400 mg/d) in combination with either fluoxetine (up to 40 mg/d) or fluvoxamine (up to 100 mg/d) for a period of 10 days (65,253). No serious adverse events were reported. Similar results were found in 18 healthy subjects when moclobemide (600 mg) or placebo has been replaced by fluoxetine (20 to 40 mg/d) for 23 days (69).

No serious adverse effects were reported in small retrospective studies on patients with depression who received either fluoxetine and moclobemide (116), or moclobemide and fluoxetine, fluvoxamine or paroxetine (15,77). Delini-Stula et al. (57), however, described one serotonin syndrome during concomitant administration of moclobemide with various SSRIs. Clinical concern was raised by an open study of Hawley et al. (106). In this study, moclobemide (600 mg/d) was combined with either paroxetine or fluoxetine in patients with treatment-resistant depression. In 50 patients studied, there was a high rate of severe adverse events including one definite serotonin syndrome. Most common adverse effects were insomnia, dizziness, headache, vomiting, nausea, ataxia, myoclonic jerks and prostration (106).

Quality-of-Life Analyses

Health Related Quality Of Life (HRQOL) is commonly impaired in patients with affective disorders (150,254). Two trials investigated the effect of moclobemide on HRQOL of depressed patients (150,252). Walker et al. (252) investigated 651 patients treated over a period of 8 weeks with moclobemide (300 to 450 mg/d). They described a significant improvement in the General Health Questionnaire (GHQ) and in the following domains of the SF36: emotional functioning, social functioning, mental health and vitality. A change in the body pain-domain of the SF36 was not statistically significant (252). Lonnqvist et al. (150) reported on a comparable improvement of the HRQOL of depressed patients during treatment with either fluoxetine (20 to 40 mg/d) or moclobemide (300 to 450 mg/d). The improvement started at week 2 of the treatment and increased progressively (150).

DOSAGE AND ADMINISTRATION

Most studies used daily doses of moclobemide in the range of 300 to 600 mg which were found to be therapeutic. These oral doses were usually given in 2 to 3 divided doses. One controlled study found that at 150 mg b.i.d. moclobemide was as effective as at 100 mg t.i.d. (89). At daily moclobemide doses for up to 900 mg/d no dietary tyramine restriction is required (68). However, large amounts of tyramine-rich food (53, 54) should be avoided (e.g., >50g of mature or overripe cheese) and moclobemide should be taken at the end of a meal to minimize the interaction with ingested tyramine. The relatively short plasma elimination half-life of moclobemide allows a switch to other antidepressants within 24 h (159). Dosage modifications for patients with renal dysfunction are not needed (205), but should be considered for patients with severe hepatic impairment. In this population, dosage should be reduced by 50% (227). Moclobemide should be used with caution in patients who receive serotonergic drugs, but is regarded as safe in patients with cardiovascular diseases. Switching from other antidepressants to moclobemide within 24 h was generally assumed to be safe (66). However, the immediate switch from fluoxetine to moclomemide is associated with a risk of the serotonin syndrome (57).

PLACE IN THE MANAGEMENT OF DEPRESSION AND ANXIETY DISORDERS

Nearly all meta-analyses and most comparative studies indicated that moclobemide is more efficacious than placebo and as efficacious as tricyclic (or some heterocyclic) antidepressants or SSRIs in the acute management of depression (Table 9). However, as with most other antidepressants, it should be realized that there were only a few three-way studies comparing moclobemide with another antidepressant and placebo (14,136,169, 209,245,249). Half of these studies found that either drug was superior to placebo (14,245, 249) and the other half found that moclobemide was not superior to placebo (136,169, 209). To date, there exists no three-way study comparing moclobemide with a SSRI and a placebo. It is striking that most relevant clinical studies on moclobemide were published in journal supplements. Some trials reported on an earlier onset of antidepressant action of moclobemide; these findings have not been confirmed in a recent meta-analysis comparing moclobemide and fluoxetine (219). In subgroup analyses, moclobemide was not found to be inferior to other antidepressants in the treatment of dysthymia, endogeneous (uni- and bipolar), reactive, atypical, agitated or retarded depression (9–12,58). The only available controlled study on bipolar depression revealed a lower incidence of manic symptoms in patients on moclobemide (3.7%) than on imipramine (11%), although the difference did not reach statistical significance (210). This study also found moclobemide to be as efficacious as imipramine in bipolar depression (210). Another larger trial supported the efficacy of moclobemide in dysthymia (249). Higher doses of moclobemide might enhance its efficacy in a more severe depression (12,153). But at moclobemide doses above 900 mg per day the risk of interaction with ingested tyramine might become clinically relevant (68).

There is a lack of controlled clinical studies addressing the long-term efficacy of moclobemide. Nevertheless, there is a limited but consistent evidence to support the long-

term efficacy of moclobemide in depressed patients (89,143,162,164). Refractory depression might profit from the combination of moclobemide and clomipramine or a SSRI, though this combination is associated with the risk of the potentially fatal serotonin syndrome.

While one controlled trial (217) and one long-term study (250) found moclobemide to be markedly efficacious in social phobia, three subsequent controlled trials revealed no or less robust effects (113,176,204). There was, however, a tendency for moclobemide at higher doses (600–900 mg/d) to be more efficacious. Although placebo-controlled trials are lacking, two comparative trials demonstrated moclobemide to be as efficacious as fluoxetine or clomipramine in patients suffering from panic disorder (132,237).

Adverse effects of moclobemide are comparable to those seen with SSRIs. Moclobemide is much better tolerated than tri- or heterocyclic antidepressants because anticholinergic side effects of moclobemide are negligible. Moclobemide is, therefore, particularly attractive in the treatment of elderly patients. Disturbances of sexual function are negligible with moclobemide as compared to tri- and heterocyclic antidepressants or SSRIs. There was no increase in bodyweight throughout a large long-term trial with moclobemide (164). This finding might improve patients compliance. Furthermore, moclobemide lacks significant negative effects on psychomotor performance and cognitive function and would, therefore, not requirea ny driving restrictions.

In comparison with classical MAO inhibitors, moclobemide's interaction with tyramine is minimal. It has been shown that at a daily dose of moclobemide up to 900 mg the usual dietary precautions are dispensable. However, large amounts of tyramine-rich foods,

*TABLE 9. Response rate to antidepressants as compared to placebo in controlled trials**

	Response rate[a] (% of patients)	
	Drug	Placebo
Tricyclic antidepressants (*N* = 3327)[b]		
Amitriptyline	60	25
Amoxapine	67	49
Imipramine	68	40
Serotonin reuptake inhibitors (*N* = 2463)[b]		
Paroxetine	45	23
Fluoxetine	60	33
Fluvoxamine	67	39
Sertraline	79	48
MAO inhibitors (*N* = 1944)[b]		
Phenelzine	64	30
Moclobemide	64	24
Noradrenergic and specific serotonergic antidepressants (*N* = 277)[c]		
Mirtazapine	48	20

* Adapted from references 55 and 80a.

[a] HAM-D scores, after 4–6 weeks of treatment.

[b] Total number of patients included in placebo-controlled and/or comparison trials.

[c] Data on file, Organon, Inc., West Orange, NJ.

such as mature cheese, yeast extracts and fermented soya should be avoided. As a further precaution, it is advised that moclobemide should be taken at the end of a meal. Furthermore, drug interactions with moclobemide are less of a problem than with traditional MAO inhibitors (23,29,118,141).

There is an increasing evidence that overdoses of moclobemide are relatively safe. This is an important consideration in the treatment of depression where there is always a risk of suicide.

The drug has a relatively short plasma elimination half-life that allows a change to an alternative antidepressant within 24 h, an advantage for non-responders.

Similarly to other antidepressants, moclobemide therapy is not without risk, especially in respect to the serotonin syndrome when moclobemide is combined with serotonergic agents. However, the overall profile of moclobemide in terms of its few adverse effects and absence of negative effects on psychomotor and cognitive performance suggests that benefits outweigh the disadvantages of its use in patients suffering from depression or circumscribed anxiety disorders.

Moclobemide appears not be inferior to tricyclics or SSRIs in its central effects (Table 10) and may be especially suitable for the treatment of patients with depression who suffer from concomitant cardio- or cerebrovascular diseases, epileptic disorders, social phobia, panic disorder, or sexual dysfunction.

Abbreviations

ACE, Adverse Clinical Events
ADHD, Attention Deficit Hyperactivity Disorder
cAMP, Cyclic Adenosine Monophosphate
CGI, Clinical Global Impression Assessment
CNS, Central Nervous System
CYP, Cytochrome P450
DA, Dopamine
DAUG, Danish University Antidepressiva Study Group

*TABLE 10. Quality assessment of antidepressants**

Parameter	TCA	SSRI	RIMA
Efficacy	++	++	++
Speed of onset of the antidepressant effect	+	+	+
Stability of the antidepressant effect in long-term treatment	+(?)	+(?)	+(?)
Acceptability of treatment	++	++	++
Tolerability	+	++	++
Side effects at therapeutic doses	++	+	+
Safety[a]	+	++	++
Price	+	++	++

* Adapted from ref. 228.

[a] With respect to toxicity in overdose, dangerous side effects at therapeutic dose and interactions.

Abbreviations: TCA, tricyclic antidepressants; ?, questionable; +, present, moderate; ++, pronounced, definite.

5-HT, 5-Hydroxytryptamine (Serotonin)
GABA, Gamma-Amino-Butyric-Acid
GHQ, General Health Questionnaire
HAM-A, Hamilton Anxiety Rating Scale
HAM-D, Hamilton Depression Rating Scale
HPA, Hypothalamic Pituitary Adrenocortical Axis
HPLC, High-Performance Liquid Chromatography
HRQOL, Health Related Quality of Life
IMMS, International Multicenter Trial Group on Moclobemide in Social Phobia
ITT, Intention-To-Treat
LSAS, Liebowitz Social Anxiety Rating Scale
MADRS, Montgomery–Asberg Depression Rating Scale
MAO, Monoamine-Oxidase Enzymes
NA, Noradrenaline (Norepinephrine)
NMDA, *N*-Methyl-D-Aspartate
REMS, Rapid Eye Movement Sleep
RIMAN, Reversible Inhibitor of Monoamine-Oxidase-A
Ro 12-5637, Metabolite of moclobemide (N-Oxide)
Ro 12-8095, Metabolite of moclobemide (C-Hydroxide)
SSRIs, Selective Serotonin Reuptake Inhibitors
TCA, Tricyclic Antidepressants

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